REMARKS

Applicants have amended the specification of delete the claim or priority to, US Application 09/380137 filed 8/25/1999, which is the National Stage filed under 35 U.S.C. § 371 of PCT Application PCT/US99/12252 filed 6/2/1999, which claims priority under 35 U.S.C. § 119 to US Provisional Application 60/088030 filed 6/4/1998.

Applicants thank the Examiner for the review of the instant application. Claims 1-5 are presented for examination. Applicants respond below to the specific rejections raised by the PTO in the Office Action mailed June 27, 2006. For the reasons set forth below, Applicants respectfully traverse.

Rejection Under 35 U.S.C. §101 – Utility

The PTO maintains its rejection of Claims 1-5 under 35 U.S.C. § 101 as lacking a specific and substantial asserted utility or a well established utility. The PTO states that the specification fails to disclose enough information about the invention to make its usefulness immediately apparent. The PTO also states that Applicants' evidence that differential expression of PRO874 mRNA in tumor tissue relative to normal tissue is insufficient evidence that the claimed PRO874 antibody will function as a cancer diagnostic.

For the reasons set forth below, Applicants respectfully disagree.

Applicants incorporate by reference their previously submitted arguments, and for the reasons of record assert that the specification contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented and therefore must be taken as sufficient to satisfy the utility requirement of 35 U.S.C. § 101. Applicants also submit that for reasons of record, the PTO has not met its burden of providing evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility. However even if the PTO has met its initial burden, Applicants' rebuttal evidence previously submitted and additional evidence submitted herewith is sufficient to prove that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true.

As stated previously, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. Even if the correlation between Applicants evidence and the asserted utility is not exact, such that there are exceptions to the correlation between the evidence and the asserted utility, this is sufficient to establish a

utility. *See Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (stating that "a 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' suffices," and thus a utility was established even though there were exceptions to the correlation between the disclosed *in vitro* data and asserted *in vivo* utility). Therefore, exceptions between the evidence disclosed and the asserted utility is permissible – **the standard is not absolute certainty.**

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

In an attempt to clarify Applicants' argument, Applicants offer a summary of their argument and the disputed issues involved.

1. Applicants have provided reliable evidence that mRNA for the PRO874 polypeptide is expressed at least two-fold higher in normal lung tissue compared to lung tumor;

2. Applicants assert that it is well-established in the art that differential expression levels of an mRNA for a particular protein, e.g. lower in tumor vs. normal, generally leads to corresponding differential expression levels of the encoded protein, e.g. lower in tumor vs. normal;

3. Given Applicants' evidence that the level of mRNA for the PRO874 polypeptide is differentially expressed in lung tumors compared to normal lung tissue, it is likely that the PRO874 polypeptide is similarly differentially expressed in lung tumors compared to normal lung tissue. Antibodies to polypeptides such as PRO874 which are differentially expressed in certain cancers are useful as diagnostic tools, alone or in combination with other diagnostic tools.

Applicants understand the PTO to be making several arguments in response to Applicants' asserted utility:

1. The PTO challenges the reliability of the evidence reported in Example 18, stating that "[t]here is no evidence of record that PRO874 transcripts were measured accurately or that the changes seen were consistent and reproducible. The skilled artisan would not know if the changes seen were disease-dependent or disease-independent." *Office Action* at 8, citing Hu *et al.* (J. Proteome Res. 2003; 2(4):405-12) and LaBaer (Nature Biotechnol. 2003; 21(9):976-7) for support;

2. The PTO argues that "[b]ecause there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis the skilled artisan would not know if the disclosed change in PRO874 mRNA transripts is associated with a corresponding change in the level of PRO874 protein. Hence, the skilled artisan would not know if or how PRO874 polypeptide expression would change in cancer." *Office Action* at 5; citing Haynes *et al.* (Electrophoresis, (1998) 19(11):1862-71); Allman *et al.* (Blood, (1996) 87(12):5357-68); Molecular Biology of the Cell, 3rd ed. (Exh. 1, 8/10/2005); Molecular Biology of the Cell, 4th ed. (Exh. 4, 12/10/05); Genes VI (Exh. 3, 8/10/05); Polakis Declaration (Exh. 3, 12/10/05); and Meric (Exh. 5, 8/10/05).

Applicants respectfully submit that in light of all of the evidence, the PTO's arguments are not adequate to support the utility rejection of the claimed invention under 35 U.S.C. § 101.

The PTO has Concluded that the data in Example 18 are Sufficient to Establish the Utility of the Claimed Invention

As an initial matter, Applicants point out that in other applications filed by Applicants that rely on *data from the exact same disclosure, Example 18*, and in which the Applicants have submitted *substantially the same references* in support of their asserted utility, the PTO has concluded that:

> Based on the totality of evidence of record, **one of skill in the art would find it more likely than not that an increase in message as measured by RTPCR would be predictive of an increase in protein expression levels,** absent evidence to the contrary. Therefore, the data presented in Example 18, which demonstrates differential expression of nucleic acids encoding PRO1180, also supports a conclusion of differential expression of PRO1180 polypeptide. Therefore, one of ordinary skill in the art would be able to use the PRO1180 polypeptide diagnostically for distinguishing normal kidney and rectal tumor tissues compared to kidney tumor and normal rectal tissue, as asserted by Applicant. *Examiner's Reasons for Allowance, Application No. 10/063,529* (emphasis added).

See also *Examiners Reasons for Allowance* in Application No. 10/063,530, No. 10/063,524, No. 10/063,582, and No. 10/063,583, all of which conclude that the data presented in Example 18, which demonstrate differential expression of the nucleic acids encoding certain PRO polypeptides, also support a conclusion of differential expression of the PRO polypeptides,

making the claimed PRO polypeptides and antibodies that bind the PRO polypeptides useful for diagnostic purposes.

Applicants therefore request that the Examiner recognize the utility of the claimed invention, supported by the data presented in Example 18 and the numerous cited references, as was done in the other applications referenced above.

Applicants have established that the Gene Encoding the PRO874 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue

Applicants submit that the gene expression data provided in Example 18 of the present application are sufficient to establish that the PRO874 gene is differentially expressed in lung tumor tissue as compared to normal lung tissue, and is therefore useful as a diagnostic tool for lung cancer. This assertion is based on the results of RT-PCR analysis of pooled normal lung tissue and pooled lung tumor tissue using methods that are well-established in the art.

This utility is substantial, *i.e.* distinguishing tumor cells from normal cells is not an insubstantial or trivial utility without a real world use, and it is specific, *i.e.* it is directed to specific disease and is not a utility that the entire class of nucleic acids shares. Finally, this asserted utility is credible, as one of skill in the art would readily believe that a nucleic acid sequence can be used as a marker to distinguish tumor tissue from normal tissue.

Applicants remind the Examiner that Applicants enjoy a presumption that their assertions are true. The Examiner must approach Applicants' assertion of utility as being sufficient to satisfy the utility requirement. M.P.E.P. §2107.02, "Procedural Considerations Related to Rejections for Lack of Utility," states:

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope. *M.P.E.P. §2107.02* at III. A., *quoting In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (C.C.P.A. 1974) (emphasis in original).
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> Thus, *Langer* and subsequent cases direct the Office to presume that a statement of utility made by an applicant is true. ... Office personnel should not begin by questioning the truth of the statement of utility. Instead, any inquiry must start by

> asking if there is any reason to question the truth of the statement of utility. ... Clearly, Office personnel should not begin an evaluation of utility by assuming that an asserted utility is likely to be false, based on the technical field of the invention or for other general reasons. *Id.*

With respect to the use of the PRO874 nucleic acid to distinguish tumor from normal tissue, the Examiner must accept this assertion as true "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility." Therefore, the question is whether the PTO has established that there is a reason to doubt the objective truth of Applicants' assertion that using standard RT-PCR procedures to examine the expression of the PRO874 mRNA in pooled normal lung samples and pooled tumor lung samples, Applicants discovered that PRO874 mRNA is differentially expressed between normal and tumor such that it can be used as a diagnostic tool.

In response to Applicants' asserted utility, the PTO asserts that "[t]he skilled artisan would not know if the changes seen were disease-dependent or disease-independent." *Office Action* at 8. This assertion is based on three sentences from a letter to the editor by LaBaer about the Hu reference, and a related statement in the Hu *et al.* reference, of which LaBaer was the primary investigator:

> In the accelerating quest for disease biomarkers, the use of high-throughput technologies, such as DNA microarrays and proteomics experiments, has produced vast datasets identifying thousands of genes whose expression patterns differ in diseased versus normal samples. Although many of these differences may reach statistical significance, they are not always biologically meaningful. For example, reports of mRNA or protein changes of as little as two-fold are not uncommon, and although some changes of this magnitude turn out to be important, most are attributable to disease-independent differences between the samples. *LaBaer* at 976.

> It is not uncommon to see expression changes in microarray experiments as small as 2-fold reported in the literature. Even when these expression changes are statistically significant, it is not always clear if they are biologically meaningful. *Hu* at 411, right column, first full paragraph.

Thus, the PTO is arguing that because "high throughput technologies, such as DNA microarrays" produce differences in mRNA that are attributable to "disease-independent differences between samples," this establishes "a reason for one skilled in the art to question the objective truth" of Applicants' asserted utility which is based on RT-PCR analysis of pooled samples of normal and tumor tissue, not microarrays.

Applicants respectfully submit that one of skill in the art would not accept that the PTO has established a basis to doubt Applicants' asserted utility. As Applicants' have previously stated, those of skill in the art recognize that RT-PCR is a more accurate and reliable technique than microarrays (see, e.g., Kuo *et al.*, (Proteomics 2005; 5(4):894-906), previously submitted). Therefore, it would be readily apparent to one skilled in the art that opinions regarding data from high-throughput techniques such as microarrays are simply not relevant to Applicants' RT-PCR data, and are not a reason to doubt the truth of Applicants' asserted utility. Thus, even if accurate, a point which Applicants do not concede, Hu's and LaBaer's opinions regarding microarray studies are not relevant to the utility of the instant application which does not rely on microarray data.

Applicants emphasize that they are not asserting that microarray data are not reliable (that is apparently the PTO's position based on Hu and LaBaer), merely that Applicants are using a method that is recognized by those of skill in the art as more reliable and sensitive.

In response to Applicants' previous arguments based on Kuo, the PTO states that Kuo is not persuasive because "it cannot be ascertained if Kuo's microarray data was [*sic*] consistent or inconsistent with Kuo's RT-PCR data. Kuo's poor correlation between microarray and proteomic expression profiles does not speak to changes in mRNA attributable to disease-independent differences between samples." *Office Action* at 2.

The PTO's argument misses the point of Applicants' reliance on Kuo. Kuo is cited as evidence to support Applicants' assertion that Applicants' PCR data are more accurate and reliable than the microarray technique commented on by Hu and LaBaer. Kuo supports this assertion because it is evidence that one of skill in the art would regard PCR as a more accurate and reliable method of assessing changes in mRNA. Thus, whether or not the microarray technique commented on by Hu and LaBaer yields "disease-independent" results is not relevant to Applicants' data because, as evidenced by Kuo, PCR data such as Applicants' are more accurate and reliable than the microarray data relied on by Hu and LaBaer. Until the PTO provides evidence that transcript changes detected by PCR analysis of pooled normal and tumor samples are often "disease-independent," the PTO's rejection of the data in Example 18 based on Hu and LaBaer is misplaced, and Applicants' asserted utility must be presumed true.

Applicants also note that neither Hu nor LaBaer cite any references to support their assertions that "most [microarray differences] are attributable to disease-independent differences

between the samples" and that "it is not always clear if [the microarray differences] are biologically meaningful." In the absence of any supporting references, Applicants cannot independently evaluate these statements to determine what is meant by "disease-independent differences" and "biologically meaningful." Read in light of the entire article and accompanying letter to the editor, Applicants assert that these statements should be interpreted to mean that the observed differences do not play a role in the development or progression of the disease state, or that such a role in the disease state has not yet been published. As Applicants have previously stated, a differentially expressed mRNA can serve as a marker of a disease even if it is "disease-independent" in the sense that it has no role in the cause or progression of a disease, or if any such role is not yet published in the literature. Applicants invite the PTO to provide support for an alternate interpretation of "disease-independent" as used in Hu and LaBaer.

With respect to Applicants' arguments that Hu and LaBaer are silent regarding the reliability of pooled samples, which are incorporated herein by reference, the PTO states:

> In practicing the invention some value for PRO874 polypeptide expression must be obtained in order to distinguish normal tissue from tumor tissue. Establishing a cutoff value for this distinction would be difficult unless one knows the typical degree of variation within the pool, which applicants have not provided. There is no evidence of record concerning the normal range in PRO874 mRNA levels or PRO874 polypeptide levels. There is no evidence of record that a normal range of PRO874 mRNA or PRO874 polypeptide levels could be defined that would distinguish normal tissue from tumor tissue. Without knowledge of the typical degree of variation within the pool one would not know if any particular measurement from a tissue would indicate normal tissue or tumor tissue. Pooled samples would also obscure the variation between samples, making the disclosed results for PRO874 polynucleotide expression less useful, accurate and informative than if results from individual samples had been provided. In fact, the range of values from normal and/or tumor tissue could be so broad that it would be impossible to distinguish normal tissue from tumor tissue. *Office Action* at 3-4.

The PTO presents no evidence to support these assertions. Thus, the PTO uses conclusory and unsupported arguments as the basis for dismissing the declaration of an expert. As such, the PTO's position is inconsistent with the Utility Examination Guidelines which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered" (*66 Fed. Reg.*

1098, Part IIB (2001)) and also is inconsistent with the requirement of the PTO to support its assertions of fact. *See In re Zurko*, 258 F.3d 1379, 1385, 59 USPQ2d 1693, 1697 (Fed. Cir. 2001). Absent supporting evidence, it is inappropriate for the PTO to dismiss Applicants' arguments and Mr. Grimaldi's opinion regarding pooled samples simply because the PTO wishes to take a contrarian position on the use of pooled samples in diagnostics.

Regarding the substance of the above-quoted text from the PTO regarding pooled samples, Applicants traverse this position and maintain that their expert has established that "[d]ata from pooled samples is more likely to be accurate than data obtained from a sample from a single individual." *First Grimaldi Declaration* at ¶5. As to the PTO's statement that "[i]n fact, the range of values from normal and/or tumor tissue could be so broad that it would be impossible to distinguish normal tissue from tumor tissue," (*Office Action* at 4, emphasis added), Applicants note that the Grimaldi declaration make clear that, in fact, "the results of the gene expression studies indicate that the genes of interest can be used to differentiate tumor from normal." *First Grimaldi Declaration* at ¶7. Applicants refrain from further rebutting the PTO's assertions because there presently are no facts on the record to support a position other than that of Mr. Grimaldi's. Applicants respectfully request that the PTO provide evidentiary support for its assertions regarding pooled samples in order to fully develop these issues under examination.

As for the PTO's statement that the first Grimaldi declaration is "in contrast with the specification's teachings," (see *Office Action* at 3), Applicants do not know how to respond since the Office has not explained how the declaration is in contrast with the quoted portion of the specification or what relevance any contrast between the two statements has to Applicants' asserted utility. Similarly, the Office's statement that "Hu and LaBaer are evidence that a skilled artisan would consider the precise level of PRO874 gene expression as relevant" is not supported by any reasoning or citation to Hu and LaBaer. Applicants' are unaware of any teaching in Hu and LaBaer regarding the need for a "precise level of PRO874 gene expression" to use it as a molecular marker to distinguish tumor tissue from normal tissue. In fact, Hu and LaBaer teach nothing at all regarding developing diagnostic markers of cancer.

In conclusion, Applicants submit that the evidence reported in Example 18, supported by the first Grimaldi Declaration, establish that there is at least a two-fold difference in PRO874 mRNA between lung tumor tissue as compared to normal lung tissue. Applicants' assertion that PRO874 mRNA can be used to distinguish lung tumor tissue from normal lung tissue must be

presumed true by the Examiner unless there is a reason that one of skill in the art would doubt the objective truth of Applicants' statements. Applicants have shown that the references by Hu and LaBaer are inapplicable to Applicants' RT-PCR data, and the PTO has provided no evidentiary basis for dismissing the Grimaldi Declaration. Thus, any challenge to the sufficiency of the data with respect to the utility of the nucleic acid is inappropriate.

Therefore, the only issue which remains is whether the data in Example 18 regarding differential expression of the PRO874 mRNA are reasonably correlated with differential expression of the PRO874 polypeptide such that the claimed antibodies have utility as diagnostic tools as well. As discussed below, even if the PTO has established a reasonable doubt regarding Applicants' assertion that they are reasonably correlated, Applicants' overwhelming rebuttal evidence is more than sufficient to establish that changes in mRNA level lead to corresponding changes in protein level.

The PTO's Evidence is Not Relevant to Determining Whether a Change in mRNA Level for a Particular Gene leads to a Corresponding Change in the Level of the Encoded Protein

Applicants turn next to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a change in the level of mRNA encoding a particular protein generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO874 polypeptide in lung tumors, it is likely that the PRO874 polypeptide is also differentially expressed; and proteins differentially expressed in certain tumors, and antibodies that bind such proteins, have utility as diagnostic tools. As stated above, the Examiner should approach these assertions of utility with a presumption that they are true.

In response to Applicants' assertion, the PTO cites, among others, Haynes *et al.* (Electrophoresis, 1998; 19(11):1862-71), Gygi *et al.* (Mol. and Cell. Bio., 1999; 19(3):1720-30), Allman *et al.* (Blood, 1996; 87(12):5357-68), Chen *et al.* (Mol. Cell. Proteomics, 2002; 1:304-13) and Hancock (J. Proteome Res., 2004; 3(4):685), as well as several references relied on by Applicants, Molecular Biology of the Cell, 3rd ed. (Exh. 1, 8/10/2005); Molecular Biology of the Cell, 4th ed. (Exh. 4, 12/10/05); Genes VI (Exh. 3, 8/10/05); Polakis Declaration (Exh. 3, 12/10/05); and Meric (Exh. 5, 8/10/05) for support of its argument that "the skilled artisan would not know if or how PRO874 polypeptide expression would change in cancer." *Office Action* at 5.

Applicants have previously discussed at length why the Haynes, Gygi, Allman and Chen references are not relevant to the issue of whether differential mRNA expression levels for a particular gene lead to corresponding differential expression of the encoded protein. Applicants incorporate by reference the previous arguments, and will not repeat them here. However, in an attempt to illustrate why references which relate to static global levels of mRNA and protein across different genes are not relevant to Applicants' asserted utility, Applicants provide the following.

Haynes and Gygi looked for a correlation between the level of mRNA and corresponding protein by plotting a single measurement of mRNA level vs. protein level for a large group of different genes. The only way that such a plot would result in a significant correlation is if there exists a global ratio between mRNA levels and protein levels common across all genes, i.e., that for every X copies of an mRNA, there are Y copies of the encoded protein, such that the ratio of X:Y is constant across all genes. The data of Haynes and Gygi indicated that the steady state ratio of mRNA:protein level varied for different genes, and hence no global ratio existed. Based on this, the references concluded that protein levels cannot be accurately calculated from mRNA levels, and that "it is evident that the analysis of mature protein products in cells is essential as there are numerous levels of control of protein synthesis, degradation, processing and modification." *Haynes* at 1863, right column, full paragraph 2.

In contrast, Applicants' asserted utility does not require knowledge of or even the existence of a global ratio between mRNA levels and protein levels. Nor do Applicants' assertions require calculation of protein levels based on measured mRNA levels. Unlike Haynes and Gygi, Applicants are not relying on a single measure of mRNA for a particular gene and then attempting to calculate protein levels based on a global ratio between mRNA and protein levels. Instead, Applicants are relying on differential mRNA expression, where mRNA levels are measured in two different conditions, i.e. tumor and normal. Applicants assert that a change in mRNA expression level for a particular gene typically lead to a corresponding change in the expression level of the encoded protein. *See, e.g., First Grimaldi Declaration* at paragraph 7. The Haynes and Gygi references are applicable only to a completely unrelated issue – whether a single measure of mRNA levels can be used to predict protein levels – and therefore, none of the data or conclusions of these references have any bearing on Applicants' assertions.

To exemplify the difference between these references and Applicants' asserted utilities, Applicants offer the following illustration and analogy with the understanding that like all illustrations and analogies, they are not perfect and therefore do not represent any admissions or binding statements regarding Applicants' disclosure or invention.

Haynes and Gygi discuss whether there is a correlation between a single measure of mRNA and protein level globally, *i.e.* across different genes at a given time. This is equivalent to conducting a hypothetical Experiment 1, where a particular cell type has 100 copies of mRNA for gene X, 200 copies of mRNA for gene Y, and 400 copies of mRNA for gene Z. If there is a global correlation between static mRNA levels and protein levels across genes, the ratio of the amount of proteins X:Y:Z would be approximately 1:2:4. This is essentially what the cited references examined.

In contrast, Applicants are relying on a correlation between changes in mRNA level for a particular gene leading to a corresponding change in the level of the encoded protein when comparing tissues at two different times or conditions. For example, in hypothetical Experiment 2, if gene X has 100 copies of mRNA per cell in condition A (*e.g.* normal), and 200 copies of mRNA for gene X in condition B (*e.g.* tumor), the amount of protein X in condition A would be smaller than the amount of protein X in condition B, for example, having a ratio of 1:2, such that there is a correlation between the difference in the level of mRNA and the difference in the level of protein for a particular gene.

The PTO argues that because there is no correlation between levels of mRNA and protein across genes at a particular time, as illustrated by Experiment 1, one of skill in the art would not expect an increase or decrease in the amount of mRNA for a particular gene to result in a corresponding change in the amount of the encoded protein, as illustrated in Experiment 2. This is simply wrong – there does not need to be a global correlation across genes for there to be a correlation in changes for a particular gene.

For example, Haynes reports that the amount of protein produced by similar levels of mRNA varied by as much as fifty-fold, and that similar amounts of protein were sustained by amounts of mRNA that varied by as much as forty-fold. *Haynes* at 1863, first full paragraph. Based on these results, Haynes concludes that "protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript." *Id.*

This is analogous to a finding that on one gallon of gas, a hybrid car can travel 50 miles but a large truck can only travel 5 miles, or that to travel 50 miles, a hybrid car requires 1 gallon of gas, but a large truck requires 10 gallons. That is to say, there are many things which affect the fuel efficiency of an automobile. Based on these observations, one could conclude that given the lack of a global ratio of gas to miles, and the resulting lack of correlation between the amount of gas in an automobile and the distance it travels, one cannot predict how far an automobile will travel based on the amount of gas in the tank.

Even if true, Haynes' data and conclusions are irrelevant to Applicants' assertion, which is that increasing or decreasing the amount of mRNA for a particular gene will result in a corresponding increase or decrease in the amount of the encoded protein. This is analogous to increasing or decreasing the amount of gas in an automobile – it will travel farther if you add more gas, and not as far with less. The fact that there are many things which affect fuel efficiency and therefore you cannot predict how far and automobile will travel without knowing if it is a hybrid or a large truck is irrelevant – both a hybrid and a truck travel farther on more gas, and not as far on less.

Applicants emphasize, and the PTO will recognize, that these are simplified illustrations to demonstrate the difference between the two issues being examined. However, these illustrations make clear that even if there is no correlation in the first experiment looking at static levels of mRNA and protein across genes, there can still be a correlation between changes in mRNA and protein for a particular gene as examined in the second experiment.

The PTO also relies on Allman as an example of a lack of correlation between mRNA expression and protein expression levels. As Applicants have previously pointed out, Allman teaches that for cells expressing higher levels of BCL-6 mRNA, BCL-6 polypeptide levels also were higher, relative to BCL-6 polypeptide levels in cells that expressed lower levels of BCL-6. Nowhere does Allman teach that a change in mRNA levels would not lead to a corresponding change in levels of the encoded polypeptide. Accordingly, Allman is not contrary to Applicants' asserted utility and does not support the PTO's position, and provides teachings consistent with Applicants' asserted utility.

In response, the PTO argues:

> If one is to argue, as applicants have argued, that because PRO874 transcripts are differentially expressed in tumors it is more likely than not that the PRO874 polypeptide is differentially expressed in tumors, and therefore PRO874

> polypeptide and antibodies can be used for tumor diagnosis, then one must also accept the argument that because resting B cells and germinal center B cells express similar BCL-6 mRNA levels it is more likely than not that the BCL-6 protein is not differentially expressed in these two cell populations, and therefore BCL-6 protein and antibodies thereto cannot be used as a marker for germinal center B cells. One must also accept the argument that because germinal center B-cells express dramatically more BCL-6 protein than resting B cells it is more likely than not that BCL-6 mRNA is differentially expressed in these two cell populations, and therefore BCL-6 mRNA can be used as a marker for germinal B-cells. Allman indicates that this is not so and therefore Allman does not support applicants' position. *Office Action* at page 5-6.

Applicants are not arguing that a change in polypeptide levels generally causes changes in mRNA levels or that polypeptide levels serve as indicators of mRNA levels. This argument conflates cause and effect. Nor do Applicants argue that a change in mRNA levels is the sole cause of changes in the level of the encoded polypeptide. Applicants merely submit that one skilled in the art would expect that a change in mRNA levels for a particular gene would generally lead to a corresponding change in levels of the encoded polypeptide. Allman is consistent with Applicants' contentions because Allman teaches that for cells expressing higher levels of BCL-6 mRNA, BCL-6 polypeptide levels also were higher, relative to BCL-6 polypeptide levels in cells that expressed lower levels of BCL-6 mRNA. Accordingly, Allman does not support a rejection of the claims for lacking utility.

Applicants next address the PTO's reliance on Chen *et al.* Applicants first note that the PTO states:

> Applicants' arguments are directed to the statement in Chen that "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (sentence bridging pages 311-312). However, this global analysis of the relationship between mRNA and protein abundance was in addition to and distinct from Chen's correlation a [*sic*] mRNA/protein abundance in the tumor samples, and the examiner did not rely on this global analysis. *Office Action* at 7.

Applicants addressed this portion of Chen because it is precisely the same kind of irrelevant study of the global relationship between mRNA and protein conducted by Haynes and Gygi which the PTO continues to rely on.

In addition to pointing out why the global analysis conducted by Chen was not relevant, Applicants also addressed the remainder of Chen in their previous responses (see *Submission*

filed with Request for Continued Examination, mailed April 6, 2006, at 14-16) which Applicants incorporate by reference. In response to these arguments, the PTO states:

> Chen statistically analyzed mRNA and protein levels (paragraph bridging pages 306 and 308). Spearman correlation coefficients of the proteins and their associated mRNA for each protein spot were generated using all 76 lung adenocarcinomas and nine non-neoplastic lung tissues (paragraph bridging pages 308-309). Figures 2A-C clearly show that for different samples a discerned change in level of mRNA is not always associated with a corresponding change in level of protein and that similar mRNA levels do not correlate with similar protein levels. *Office Action* at 7-8 (emphasis added).

Applicants have never asserted that a change in the level of mRNA is always associated with a change in protein levels. Instead, Applicants are asserting that generally, differential expression of an mRNA (e.g. tumor vs. normal) leads to a corresponding differential expression of the encoded protein. Figures 2. A-C of Chen support this assertion in that the authors conclude that for genes where a statistically significant correlation was found, like those in the figure, this "suggests that a transcriptional mechanism likely underlies the abundance of these proteins in lung adenocarcinomas." *Chen* at 313, left column. As for the other genes examined where no correlation was found, it remains unknown if there was any substantial change in mRNA levels.

Applicants next address the PTO's statement that "Applicants reference to Celis is acknowledged. However, according to Chen, Celis used proteomics and microarray analysis, which applicants have disparaged as inaccurate. Apparently, when proteomics and microarray analysis supports applicants' position it is accurate, and when it does not it is inaccurate." *Office Action* at 8.

Applicants have not disparaged microarray data or proteomics data. Applicants have merely stated that one of skill in the art would regard RT-PCR as more sensitive and reliable than microarrays, and therefore any opinions of Hu and LaBaer regarding the significance of microarray data are not applicable to Applicants' data based on RT-PCR. It is the PTO's position which is inconsistent, as the PTO relies on Hu and LaBaer to claim that microarray data are unreliable, and at the same time relies on Chen *et al.*, which uses microarray data to access changes in mRNA levels.

Finally, Applicants address the PTO's continued reliance on Hancock. Applicants incorporate by reference their previous arguments, and will not repeat them here. Additionally,

Applicants note that the PTO has not explained how Hancock's statement that "the markers that are generated by proteomics are not always consistent with the markers that are generated from expression profiling" supports the PTO's assertion that "a skilled artisan would not know if, or how, PRO874 expression would change in tumors." *Office Action* at 9.

Proteomics markers may not be consistent with expression profiling for a number of reasons. In addition to the possibility that proteomics is not sufficiently developed to accurately assess the level of protein expression, it could also be that proteomics markers are not always consistent with expression profiling markers because molecules that change at the protein level are not changing at the mRNA level. Such an inconsistency between markers is not contrary to Applicants' assertion that changes in mRNA lead to changes in protein level. As Applicants have stated numerous times, Applicants have not asserted that all protein changes reflect a change in mRNA level. Thus, absent further explanation by Hancock as to why proteomics markers are not always consistent with expression profiling, Hancock is not inconsistent with Applicants' asserted utility, and therefore cannot support the PTO's rejection.

In conclusion, Applicants have shown that the references by Haynes and Gygi are simply not relevant to the issue of whether a change in mRNA levels leads to a corresponding change in the level of the encoded protein. In addition, Applicants have shown that Allman's results are consistent with Applicants' assertions, and neither Chen nor Hancock are contrary to Applicants' assertions. Taken together, the PTO's arguments are not sufficient to satisfy the burden to "provide[] evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995).

Applicants' Evidence Establishes that a Change in mRNA Level for a Particular Gene leads to Corresponding Change in the Level of the Encoded Protein

In support of the assertion that changes in mRNA for a particular gene are positively correlated to changes in the corresponding protein level, Applicants previously submitted a copy of a second Declaration by J. Christopher Grimaldi, a copy of the declaration of Paul Polakis, Ph.D., excerpts from the Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) and (4th ed. 2002), excerpts from the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)), a reference by Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, and a reference by Meric *et al.*, Molecular Cancer

Therapeutics, vol. 1, 971-979 (2002). In addition, in the most recent response, Applicants submitted over 100 additional references in support of their assertion that changes in mRNA for a particular gene are positively correlated to changes in the corresponding protein level. The details of the teachings of these declarations and references, and how they support Applicants' asserted utility, are of record and will not be repeated here.

Applicants submit herewith a copy of a declaration by Randy Scott, Ph.D. (attached as Exhibit 1). Dr. Scott is an independent expert in the field of molecular diagnostics, with over 15 years experience. He is the author of over 40 scientific publications in the fields of protein biology, gene discovery, and cancer, and is an inventor on several issued patents. His curriculum vitae is attached to the declaration. In paragraph 10 of his declaration, Dr. Scott states:

> One reason for the success and wide-spread use of the DNA microarray technique, which has led to the emergence of a new industry, is that generally there is a good correlation between mRNA levels determined by microarray analysis and expression levels of the translated protein. Although there are some exceptions on an individual gene basis, it has been a consensus in the scientific community that elevated mRNA levels are good predictors of increased abundance of the corresponding translated proteins in a particular tissue. Therefore, diagnostic markers and drug candidates can be readily and efficiently screened and identified using this technique, without the need to directly measure individual protein expression levels. *Scott Declaration* at ¶10 (emphasis added).

Applicants submit the opinion of yet another expert in the field that changes in mRNA level for a particular protein in a given tissue generally lead to a corresponding change in the level of the encoded protein. Importantly, Dr. Scott also states that, contrary to the contentions of the PTO, diagnostic markers can be identified "without the need to directly measure individual protein expression levels." This opinion is supported by Dr. Scott's extensive experience in the field, as well as the fact that an entire industry has developed around technology to assess differential mRNA expression. As stated previously, there would be little reason to study changes in mRNA expression levels if those changes did not result in corresponding changes in the encoded protein levels.

Applicants also submit herewith a copy of a second Declaration by Dr. Polakis (attached as Exhibit 2) that presents evidentiary data in Exhibit B. Exhibit B of the Declaration identifies 28 gene transcripts out of 31 gene transcripts (i.e., greater than 90%) that showed good correlation between tumor mRNA and tumor protein levels. As Dr. Polakis' second Declaration says "[a]s such, in the cases where we have been able to quantitatively measure both (i) mRNA and (ii)

protein levels in both (i) tumor tissue and (ii) normal tissue, we have observed that in the vast majority of cases, there is a very strong correlation between increases in mRNA expression and increases in the level of protein encoded by that mRNA." Accordingly, Dr. Polakis has provided the facts to enable the PTO to draw independent conclusions.

The case law has clearly established that in considering affidavit evidence, the PTO must consider all of the evidence of record anew. *See in re Rinehart,* 531 F.2d 1084, 189 USPQ 143 (C.C.P.A. 1976); *In re Piasecki,* 745 F.2d. 1015, 226 USPQ 881 (Fed. Cir. 1985). "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument." *In re Alton,* 37 U.S.P.Q.2d 1578, 1584 (Fed. Cir. 1996), *quoting In re Oetiker,* 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). Furthermore, the Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner." *Id.* at 1583. Applicants also respectfully draw the PTO's attention to the Utility Examination Guidelines which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." *66 Fed. Reg. 1098, Part IIB (2001).*

In summary, Applicants have submitted herewith an additional expert Declaration in addition to the declarations and over 115 references already of record, which support Applicants' asserted utility, either directly or indirectly. This evidence supports the assertion that in general, a change in mRNA expression level for a particular gene leads to a corresponding change in the level of expression of the encoded protein. As Applicants have previously acknowledged, the correlation between changes in mRNA level and protein level is not exact, and there are exceptions. However, Applicants remind the PTO that the asserted utility does not have to be established to a statistical certainty, or beyond a reasonable doubt. *See M.P.E.P.* at § 2107.02, part VII (2004). Therefore, the fact that there are exceptions to the correlation between changes in mRNA and changes in protein does not provide a proper basis for rejecting Applicants' asserted utility. Applicants submit that considering the evidence as a whole, with the overwhelming majority of the evidence supporting Applicants' asserted utility, a person of skill in the art would conclude that Applicants' asserted utility is "more likely than not true." *Id.*

In conclusion, Applicants submit that they have offered sufficient evidence to establish that it is more likely than not that one of skill in the art would believe that because the PRO874 mRNA is differentially expressed in lung tumor tissue as compared to normal lung tissue, the PRO874 polypeptide will likewise be differentially expressed in lung tumors. This differential expression of the PRO874 polypeptide makes the claimed antibodies useful as diagnostic tools for cancer, particularly lung cancer.

The PTO's Position is Inconsistent with the Utility Guidelines and the Courts

In response to Applicants' evidence and arguments, the PTO takes the position that Applicants must present specific evidence directly demonstrating the utility of the claimed antibodies – specifically, direct evidence of differential expression of PRO874 polypeptide in tumor and normal tissue. Applicants submit that this requirement is inconsistent with the Utility Guidelines and the courts.

In response to the over 100 supporting references submitted in Applicants' previous response, the PTO makes the following conclusory argument:

> Exhibits 1-21 have been considered. However, none of this evidence discloses anything specific regarding PRO874 mRNA expression, PRO874 polypeptide expression, or the correlation between the two in normal tissue and tumor tissue. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO874 transcripts and PRO874 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, as evidenced by the Polakis declaration. Regarding Orntoft and Futcher, there is no evidence of record that PRO874 mRNA or protein is either abundantly expressed or abundantly under-expressed. *Office Action* at 9-10 (emphasis added, citations omitted).
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> The specification does not establish if the disclosed change in PRO874 mRNA expression is one of those cases where this [*sic*] is a correlation between a change in mRNA level and a corresponding change in the level of the encoded protein. Applicants have not provided any testing of PRO874 polypeptide expression. ... The correlation between the disclosed change in PRO874 mRNA and a change in PRO874 polypeptide expression is unknown and is not disclosed. *Office Action* at 11 (emphasis added).
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> Neither the specification nor any of Applicants' arguments, exhibits, declarations or other evidence provide any specific data disclosing if or how PRO874 polypeptide expression changes in tumor tissue. Instead, Applicants rely on a general correlation between mRNA expression and expression of the encoded protein rather than the specific correlation between PRO874 transcripts and PRO874 polypeptide expression to argue that it is more likely than not that a change in PRO874 transcripts is correlated with an assumed change in PRO874 polypeptide expression. Without any evidence of the expression of PRO874 in tumor tissue this argument is of no avail to Applicants. *Office Action* at 12-13 (emphasis added).

Thus, the PTO implies the following argument: (1) the evidence of record demonstrates that there are exceptions to the general rule that increased mRNA levels correspond to increased levels of the encoded polypeptide; (2) because such exceptions exist, it is mandatory that specific data of differential PRO874 polypeptide expression in lung tumor tissue as compared to normal lung tissue be disclosed; and (3) since such is not disclosed, the claimed antibodies that bind the PRO874 polypeptide have no substantial utility.

Adopting the PTO's standard for utility would result in a per se rule that a difference in mRNA expression cannot establish a utility for the encoded polypeptide and antibodies thereto. Thus, the PTO chooses to heighten the utility requirement to require specific, direct evidence of utility when there are exceptions to a generally accepted rule that is relied upon for utility. This heightened utility requirement is inconsistent with the Utility Guidelines and the courts. There is no requirement that utility be dispositively proven:

> Furthermore, the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." *In re Irons,* 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965) ... Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. *M.P.E.P.* 2107.02 VII (emphasis in original).

Nor is there requirement that only direct evidence of utility is sufficient to establish utility. Instead, it is established that indirect evidence that is reasonably indicative of utility is sufficient to fulfill the requirements of 35 U.S.C. §101. *Nelson v. Bowler*, 626 F.2d 853, 856. Furthermore, there is no requirement that indirect evidence necessarily and always prove actual utility. Instead, there only need be a reasonable correlation between the indirect evidence and the asserted utility. *Id.* at 857, *Cross v. Iizuka*, 753 F.2d 1040, 1050-1051. The indirect evidence

need not absolutely prove the asserted utility. All that is required is that the tests be reasonably indicative of the asserted utility. In other words, there need only be a sufficient correlation between the indirect evidence and the utility so as to convince those skilled in the art, to a reasonable probability, that the novel compound will possess the asserted utility. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564.

The PTO appears to consider the above guidance from the courts inapplicable to the present situation because in those cases the claimed compound had been tested, and, in the present test, the polypeptides to which the claimed antibodies specifically bind have not been tested. However, the PTO's position fails to recognize the issue in question for the above cases. The issue in question was whether or not Appellants' evidence (*in vitro* or animal testing of compound), which was different in nature from the asserted utility (therapeutic use of compound), was sufficient to fulfill the requirements of 35 U.S.C. §101 when there was a reasonable link between Appellants' evidence and the asserted utility. In the present case, Applicants submit that their evidence (differential mRNA expression) is reasonably linked to the asserted utility (diagnostic use of the encoded polypeptide). Insofar as it is uncontested that differential mRNA expression is reasonably linked to differential polypeptide expression, Applicants submit that such linkage is sufficient to fulfill the requirements of 35 U.S.C. §101 as provided by the guidance of the Utility Guidelines and the courts.

In conclusion, the PTO's heightened requirement for establishing utility of the presently claimed antibodies is contrary to the Utility Guidelines and the courts: it is sufficient to present evidence of differential mRNA expression since it is understood in the art that differential mRNA expression is reasonably linked to differential polypeptide expression. As discussed above, even if the PTO has presented evidence that changes in mRNA expression are not always correlated with changes in protein expression, Applicants' overwhelming rebuttal evidence is more than sufficient to establish that changes in mRNA level typically lead to corresponding changes in protein level. As such, Applicants have established that it is more likely than not that one of skill in the art would believe that because the PRO874 mRNA is differentially expressed in lung tumor tissue as compared to normal lung tissue, the PRO874 polypeptide will likewise be differentially expressed in lung tumors. Accordingly, when the evidence is applied to the proper standard for utility, it is clear that this differential expression of the PRO874 polypeptide establishes the claimed antibodies useful as diagnostic tools for cancer, particularly lung cancer.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Antibodies

Applicants next address the PTO's assertion that the asserted utilities are not specific to the claimed antibodies related to PRO874. Applicants respectfully disagree.

Specific utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO874 gene and polypeptide in lung cancer cells, along with the declarations and references discussed above, provide a specific utility for the claimed antibodies.

As discussed above, there are significant data which show that it is more likely than not that the PRO874 polypeptide is differentially expressed in lung tumor tissue as compared to normal lung tissue. These data are strong evidence that the PRO874 polypeptide is associated with lung tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO874 polypeptide with a specific disease. The asserted utility as a diagnostic tool for cancer, particularly lung tumors, is a specific utility – it is not a general utility that would apply to the broad class of antibodies.

Conclusion

Applicants remind the PTO that the evidence supporting utility does not need to be direct "specific" evidence, nor does it need to provide an exact correlation between the submitted evidence and the asserted utility. Instead, evidence which is "reasonably" correlated with the asserted utility is sufficient. *See Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565, 39 U.S.P.Q. 2d 1895 (Fed. Cir. 1996) ("a 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' suffices"); *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (same); *Nelson v. Bowler*, 626 F.2d 853, 857, 206 U.S.P.Q. 881 (C.C.P.A. 1980) (same). In addition, utility need only be shown to be "more likely than not true," not to a statistical certainty. *M.P.E.P.* at § 2107.02, part VII (2004). Considering the evidence as a whole in light of the relevant standards for establishing utility, Applicants have established at least one specific, substantial, and credible utility. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The PTO maintains its rejection of Claims 1-5 under 35 U.S.C. § 112, first paragraph. Specifically, the PTO asserts that because the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility, one skilled in the art would not know how to use the claimed invention.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed antibodies. Thus, since the enablement rejection is based on the rejection of the claims as lacking utility, Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

Rejections under 35 U.S.C. § 112, first paragraph – Written Description

The PTO has rejected Claims 1-5 as failing to comply with the written description requirement, specifically for recitation of the limitation "amino acids 34-321 of SEQ ID NO:10." The PTO argues that "[i]n the absence of any evidence that amino acid #34 is employed as a start site, the generic disclosure of what may be possible or conceivable does not convey with reasonable clarity to those skilled in the art that Applicants were in possession of the invention as now claimed." *Office Action* at 15.

Applicants submit that looking at the sequence, it would be apparent to any skilled artisan that the first methionine in SEQ ID NO:10 is likely the start methionine, and that would be sufficient evidence to convey with "reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed." *M.P.E.P.* §2163.02 (emphasis added).

For the reasons of record and those stated above, Applicants submit that the PTO has failed to meet its initial burden of "presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." *M.P.E.P.* §2163.04 (internal citations omitted, emphasis added). Applicants request that the PTO reconsider and withdraw the written description rejections under 35 U.S.C. §112, first paragraph.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Sept. 26, 2006

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